

REMARKS

I. Interview of August 17, 2010

Applicants thank the Examiner for courtesies extended at the interview with Applicants' representative on August 17, 2010. During that interview, all of the claims and outstanding claim rejections were discussed and Applicants noted evidence of unexpected results and commercial success as discussed below.

II. Status of the claims

Claims 18, 20-21, and 29-45 are pending in the application. Claims 1-17 and 22-28 are cancelled without prejudice or disclaimer. Applicants expressly reserve the right to present the subject matter of those canceled claims in future prosecution.

In this Reply, Applicants amend several claims and add one new claim. Applicants amend claim 29 merely to make it independent. Claim 29 previously depended from claim 15, which depended from claim 1. As claims 1 and 15 are now canceled, the subject matter of those two claims is now incorporated into claim 29. Applicants also amend claim 18 to depend from newly independent claim 29. Applicants rephrase claim 30 and other claims to recite that the preparation "has not been lyophilized and is not lyophilized prior to administration." Applicants make claims 35, 37, and 39 dependent on claim 29 and also make claim 40 dependent on claim 39 rather than on claim 38. Finally, Applicants add new claim 45, which is dependent on claim 39.

All of these amendments and new claims are supported by the application as a whole and include no new matter. Applicants respectfully request their entry.

Applicants also request the rejoinder of claims 18 and 20-21. Those claims were withdrawn by the Examiner as directed to non-elected subject matter. However, those claims are method claims depending from composition claim 29, which is currently under examination. Accordingly, Applicants request the rejoinder of claims 18 and 20-21 upon allowance of the composition claims.

II. The Rejections Under 35 U.S.C. §§ 102(b) and (e) Are Moot

The Examiner rejects claim 8 under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. Patent No. 5,831,736. (Office Action at pages 2-3.) As claim 8 is cancelled, that rejection is now moot and Applicants request its withdrawal.

The Examiner also rejects claims 1, 4-8, 10-13, 15-16, 23, and 28¹ under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent Application Publication No. 2005/0142139A1 (“the ‘139 publication”). (Office Action at pages 3-6.) As all of those claims are cancelled, that rejection is also moot and Applicants request its withdrawal.

III. The Rejection Under 35 U.S.C. § 103(a) based on U.S. Patent Publication No. 2005/0142139 Is Also Moot

The Examiner rejects claims 1, 7-9, and 28 as allegedly obvious under 35 U.S.C. § 103(a) in light of the ‘139 publication. (Office Action at pages 6-7.) That rejection is also moot as those claims are cancelled. Hence, Applicants request its withdrawal.

¹ The top of page 4 of the Office Action states that “the rejection of claims 29-40 has been withdrawn as the current claim amendment in claims 29, 35, 37, and 38 recite “polyclonal”.” However, the final incomplete paragraph at page 5 states that “claims 34, 36, and 40 . . . are included in this rejection . . .” Applicants presume that this is a typographical error because claims 34, 36, and 40 also recite “polyclonal IgG” or depend from claims reciting “polyclonal IgG.” Applicants further note that rejected claim 23 had previously been cancelled in the February, 2010, Reply.

IV. Claims 29-45 Are Nonobvious Over U.S. Patent No. 6,171,586 in view of U.S. Patent Publication No. 2005/0142139

Finally, the Examiner rejects claims 1, 4-13, 15-16, and 28-44 as allegedly obvious under 35 U.S.C. § 103(a) over U.S. Patent No. 6,171,586 ("the '586 patent") in view of the '139 publication. Applicants note that this rejection is moot with respect to claims 1, 4-13, 15-16, and 28, which are cancelled. Applicants traverse this rejection with respect to claims 29-44.

Several basic factual inquiries must be made to determine whether the claims of a patent application are obvious under 35 U.S.C. § 103. These factual inquiries are set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966), and require the Examiner to:

- (1) Determine the scope and content of the prior art;
- (2) Ascertain the differences between the prior art and the claims in issue;
- (3) Resolve the level of ordinary skill in the pertinent art; and
- (4) Evaluate evidence of secondary considerations.

The obviousness or non-obviousness of the claimed invention is then evaluated in view of the results of these inquiries. *Graham*, 383 U.S. at 17-18; see also *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1734 (2007). Moreover, "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusions of obviousness." M.P.E.P. § 2142 (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)); see also *KSR*, 127 S. Ct. at 1741 (quoting Federal Circuit statement with approval). "To reach a proper determination under 35 U.S.C. § 103, the Examiner must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made.

In view of all factual information, the Examiner must then make a determination whether the claimed invention ‘as a whole’ would have been obvious at the time to that person.”

M.P.E.P. § 2142.

If a *prima facie* case of obviousness is to be based upon a combination of elements, the Examiner must provide sufficient reasoning or evidence to show that the combination yields a predictable outcome or that there is a reasonable expectation of success. M.P.E.P. §§ 2143 and 2143.02. For example, even where a new combination is considered “obvious to try,” the Examiner must establish (1) that there are only a finite number of possible solutions (2) with predictable outcomes and (3) that there is a reasonable expectation of success in pursuing those possible solutions. M.P.E.P. § 2143(E).

Finally, even if a *prima facie* case is established, it may be rebutted by evidence of secondary considerations such as unexpected results and commercial success.

M.P.E.P. § 2142.

The ‘586 Patent and ‘139 Publication Do Not Apply to Polyclonal IgG Preparations and thus Do Not Motivate Use of Proline in Formulating a Polyclonal IgG

A person of ordinary skill in the art wishing to produce a new type of polyclonal IgG preparation would not turn to either the ‘586 patent or the ‘139 publication for guidance. Neither publication discloses polyclonal IgGs nor applies to polyclonal IgG preparations as Applicants claim. Accordingly, neither publication addresses the unique stability challenges encountered when trying to formulate polyclonal IgGs.

In particular, “polyclonal IgG” preparations are generally derived from pools of blood plasma from up to thousands of different individual donors. (See, e.g., D.L. Tankersley, pages 160-162; copy of article attached with the instant IDS.) As

Tankersley explains, the international regulatory agencies generally require that a polyclonal IgG preparation be derived from a large number of different individual donors, for example, 1000 or more. (*Id.* at 161.) The presence of IgG molecules from different donors within the same preparation causes stability issues that do not occur in preparations of other types of proteins, for example dimerization due to idioype-antiidiotypic interactions. (See *Id.* at 161-162, and see e.g., M. Cramer et al., at page 2, full paragraph at center of first column; and the instant specification at page 2, lines 24-26, page 10, lines 14-21, and Tables 1 and 2.) As Tankersley further explains, the dimerization is caused by antibodies from different donors, thus having different sequences, that recognize each other and bind together. (Tankersley at 161.) In contrast, polyclonal antibodies isolated from a single donor contain essentially no dimer. (Tankersley at 162.) Such dimerization can result in adverse events in patients, such as hypotension, and thus, is important to control. (See Tankersley, at page 160; specification at page 2, lines 25-32.) Polyclonal IgG preparations are also prone to aggregation, fragmentation, and oxidation. (See Cramer at paragraph bridging pages 1-2; specification at Tables 1 and 2.) Tankersley also explains that aggregation can cause dangerous adverse events such as anaphylactic shock. (Tankersley at 160-161.)

Thus, overall, one of ordinary skill in the art wishing to make a polyclonal IgG preparation at the relevant time would have been interested in controlling all four of these stability problems: idioype-antiidiotypic dimerization, aggregation, fragmentation, and oxidation. The '586 patent and '139 publication do not provide sufficient guidance on these issues because they do not disclose "polyclonal IgG" preparations.

For example, the only data or working examples provided in the '586 patent relate to attempts to formulate two specific recombinant humanized monoclonal antibodies. (See the '586 patent at cols. 24-46 and Figures 1-28.) Recombinant proteins and monoclonal antibodies do not have the stability problems associated with the claimed polyclonal IgG preparations because they comprise only one single protein species. Because they comprise only one single protein species, recombinant proteins and monoclonal antibodies cannot suffer from idiotype-antiidiotype dimerization, for example.

The Examiner contends that the '586 patent also discloses polyclonal antibody preparations. But even those polyclonal antibodies are themselves distinct from the claimed "polyclonal IgGs." For instance, the polyclonal antibodies described at column 11 of the '586 patent are obtained from host animals and directed against a "relevant antigen," in other words, against a specific antigen. ('586 patent, col. 11, at line 33.) And they may be derived from only one host animal. ('586 patent, col. 11, at lines 30-58.) Thus, such antibodies do not develop the idiotype-antiidiotype interactions that cause stability and adverse event problems for "polyclonal IgG" preparations.

In addition to those deficiencies, the Examiner acknowledges that the '586 publication also does not teach preparations comprising "a stabilizer comprising proline" as recited in claim 29, or wherein the stabilizer "consists essentially of proline," as recited in claim 41. (Office Action at page 8, last two lines.)

The Examiner cites the '139 publication for a teaching of proline. But that publication also does not teach or suggest polyclonal IgG preparations as claimed here. Instead, it deals only with a specific recombinant protein. Once again, because

recombinant proteins cannot suffer from idiotype-antiidiotype dimerization, the '139 publication provides no teaching whatsoever as to whether or not proline could stabilize a polyclonal IgG preparation.

Thus, a person of ordinary skill in the art wishing to prepare a "polyclonal IgG" preparation would not turn to either the '586 patent or the '139 publication for guidance.

Moreover, this combination of publications is not supported with the level of reasoning that is required under the Office's post-KSR guidelines. See *USPTO Examination Guidelines Update: Developments in the Obviousness Inquiry after KSR v. Teleflex*, 75 FR 53643 (Sept. 1, 2010), and M.P.E.P. § 2141. The Office Action includes only a conclusory statement that "[o]ne of ordinary skill in the art at the time the invention was made would have been motivated to [combine these documents] because the addition of proline improves stability of protein upon storage and delivery by reducing aggregation." (Office Action at page 9.) The Examiner provides no support for this statement, either in the cited publications or elsewhere in the scientific literature, and merely states that "there would have been a reasonable expectation of success in producing the claimed invention" without providing supporting reasoning. (*Id.*)

Thus, this rejection is not a *prima facie* case of obviousness. As the Office has recently pointed out, "[i]t remains Office policy that appropriate factual findings are required in order to apply the enumerated rationales [including the "TSM" test] properly. If a rejection has been made that omits one of the required factual findings, and in response to the rejection a practitioner or inventor points out the omission, Office personnel must either withdraw the rejection, or repeat the rejection including all required factual findings" such as those given above for the "obvious to try" rationale.

75 FR 53643 at 53645, col. 1 (Sept. 1, 2010). “This requirement for explanation remains even in situations in which Office personnel may properly rely on intangible realities such as common sense and ordinary ingenuity.” *Id.* at 53645, col. 2.

Because the ‘586 patent and ‘139 publication do not pertain to the instant claims and because the Office Action contains no explanation or reasoning sufficient to support this rejection, this is not a *prima facie* case of obviousness and Applicants request its withdrawal.

Even If, For the Sake of Argument, the ‘586 Patent and ‘139 Publication Disclosed Polyclonal IgG Preparations, the Teachings of Those Publications Would Not Lead One Toward the Instant, Claimed Preparations

Moreover, even if, merely for the sake of argument, the ‘586 patent and ‘139 publication were applicable to the present invention, their combined teaching would not lead one of ordinary skill toward the instant, claimed inventions. For example, the ‘139 publication

- teaches a higher pH range than claimed here (‘139 publication at paragraphs [0073], [0074], and [0126]),
- teaches that glycine and alanine are superior stabilizers than other amino acids (Tables 2-4 and 7-9; paragraphs [0032], [0039], and [0138]),
- teaches a lower concentration of amino acid stabilizer than used in many of the instant claims (paragraph [0013]), and
- and requires a histidine buffer not recited or required here (paragraphs [0008]-[0013]).

In particular, while the ‘139 publication states that its formulation may further comprise an amino acid stabilizer that could be selected from alanine, glycine, proline,

and glycylglycine, the '139 publication fails to provide any teaching or suggestion that would have prompted a skilled artisan to specifically choose proline from among the listed possibilities. To the contrary, the working examples of the '139 publication mostly contain glycine as an amino acid stabilizer and the publication explicitly states that glycine is preferred. (See *id.*, Indeed, in evaluating the effect of amino acid stabilizers, the '139 publication states that “[g]lycine and alanine showed slightly higher percentage recoveries than the other histidine-based formulation.” (*Id.*, paragraph [0138].)

Thus, if only for the sake of argument, the '586 patent and '139 publication were applicable to the rejected claims, a skilled artisan knowing nothing of the instant application would have had no motivation whatsoever to move in the direction of the present claims.

The Claimed Invention Shows Unexpected Results and Commercial Success

Finally, even if, for the sake of argument, one assumes that a *prima facie* case of obviousness has been established, the instant polyclonal IgG preparations show an unexpectedly high stability and a low level of toxic side effects. For example, the instant claims encompass Applicants' commercial product Privigen®, described in the U.S. Food and Drug Administration approved package insert (which attached with the instant IDS or can be downloaded at www.fda.gov), the article by M. Cramer et al., and the *International Blood/Plasma News* excerpt from April, 2010. Privigen® is a liquid polyclonal IgG preparation comprising about 10% polyclonal IgG formulated with 210 to 290 mM L-Proline at pH of about 4.8, and which has not been lyophilized and is not lyophilized before administration.

The attached *International Blood/Plasma News* excerpt and the Cramer et al. article both describe the exceptional stability of Privigen® compared to other available polyclonal IgG preparations. The *International Blood/Plasma News* excerpt states that “U.S. FDA has approved a supplemental Biologics License Application (sBLA) that extends the shelf life of [CSL Behring’s] *Privigen* 10% liquid intravenous immunoglobulin product from 24 months to 36 months. This approval makes *Privigen* the first liquid IVIG in the U.S. that can be stored at room temperature (up to 25°C [77°F]) throughout its entire 36-month shelf life.”

The Cramer article, written in 2008, contrasts the stability of Privigen® to that of other liquid polyclonal IgG preparations available at that time. Cramer et al. state that the “liquid IVIG formulations have limited shelf-lives. Long-term storage of liquid IVIG formulations has therefore required the use of refrigerated conditions until now.” (Page 1, column 1; Discussion, first paragraph.) For instance, the article notes that polyclonal IgG preparations at a lower IgG concentration of 5% “may be stored at room temperature for a period of up to 1 year” and that “[t]he optimal storage temperature for currently available 10% IVIG solutions is 5 °C, for a maximal storage time of 36 months [3 years]. These solutions are stable at room temperature for only a few months.” (Discussion section, first column, page 6, emphasis added.) Thus, Privigen®, despite its higher concentration of polyclonal IgG than competing liquid polyclonal IgG preparations, is about three-times more stable. (See *Id.*) And again, Privigen®’s three year, room temperature shelf life was recently approved by the U.S. Food and Drug Administration and is the longest shelf life among approved liquid polyclonal IgG preparations. (See the *International Blood/Plasma News* excerpt.)

Protein formulation is inherently unpredictable. And trial and error experimentation is generally required to determine whether a particular excipient can sufficiently stabilize a polyclonal IgG preparation against formation of dimers, aggregates, fragments, and oxidation products. (See, e.g., the Bolli Declaration at paragraphs 11-13.) Thus, one of ordinary skill in the art would not have expected that such an increase in stability of a polyclonal IgG preparation could be achieved through a stabilizer comprising proline without nicotinamide.

The instant claims also cover another commercial polyclonal IgG preparation called Hizentra™. (See the U.S. Food and Drug Administration approved package insert for Hizentra™, attached with the instant IDS, or which may be downloaded from www.fda.gov.) Hizentra™ was approved by the U.S. Food and Drug Administration in February, 2010. It is a 20% polyclonal IgG preparation comprising 210-290 mM proline and 10-30 mg/liter polysorbate 80, trace sodium, with a pH of 4.6 to 5.2, and that has not been lyophilized and is not lyophilized prior to administration. Hizentra™ is currently the most concentrated non-lyophilized polyclonal IgG preparation available on the U.S. market. And the FDA has recently extended Hizentra™'s shelf life from 18 to 24 months without refrigeration. (August 18, 2010, CSL Behring press release attached.) Due to the general unpredictability of successfully minimizing the formation of dimers, aggregates, fragments, and oxidation products in a polyclonal IgG, one of ordinary skill in the art would not have expected that, by using a stabilizer comprising proline without nicotinamide, one could achieve such a high concentration polyclonal IgG product with a two-year room temperature shelf life.

For all of the reasons given in the sections above, Applicants note that the instant claims are in condition for allowance and respectfully request the Examiner to withdraw this rejection.

V. Conclusion

In view of the foregoing remarks, Applicants submit that the claimed invention, as amended, is neither anticipated nor rendered obvious in view of the prior art references cited against this application. Applicants therefore request the entry of the above claim amendments and the timely allowance of the pending claims.

If the Examiner has questions or believes that further discussion with Applicants' representative would be helpful in advancing prosecution, the Examiner is invited to telephone Applicants' representative at her convenience to schedule an interview.

The present Reply is submitted along with a Petition for a One-Month Extension of Time, Request for Continued Examination, and associated fee payments. Please grant any extensions of time required to enter this response and charge any additional required fees not found herewith to our deposit account 06-0916.

Respectfully submitted,

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Dated: September 17, 2010

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Attachments:

Request for Continued Examination
Petition for One-Month Extension of Time
Information Disclosure Statement
PTO Form SB-08 with attached documents
Publication by M. Cramer et al., submitted with a prior IDS and SB-08